REMARKS

Claims 1-61 are pending in the application. Claims 1-8, 11-14, 18-35, 44, 45, and 50-61 have been withdrawn from consideration. In the Final Action, the Examiner did not assert the following prior rejections:

a. the rejection of claim 15 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite;

b. the rejection under 35 U.S.C. § 102(b) of claims 10, 15-17, 46, and 48 as allegedly being anticipated by U.S. Patent No. 5,721,114;

c. the rejection of claims 9, 10, 15-17, and 36 under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 96/37608;

d. the rejection of claims 9, 10, 15-17, and 36 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,258,596 B1;

e. the rejection of claims 15, 16, and 46-49 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,721,114 in view of U.S. Patent No. 5,116,964;

f. the rejection of claims 15, 16, and 46-49 under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 96/37608 or U.S. Patent No. 6,258,596 B1 each in view of U.S. Patent No. 5,116,964;

g. the rejection of claims 15, 16, and 36-43 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,721,114 in view of U.S. Patent No. 5,824,784; and

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h. the rejection of claims 15, 16, and 36-43 under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 96/37608 or U.S. Patent No. 6,258,596 B1 each in view of U.S. Patent No. 5,824,784.

The Examiner maintained the following rejections:

a. the rejections of claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification, (Final Action, pages 2-11), and as allegedly lacking written description support in the specification, (*id.*, pages 11-14);

b. the rejection of claims 15 and 46 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,408,038, (*id.*, pages 14-15);

c. the rejection of claims 15, 46, and 47 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,408,038 in view of U.S. Patent No. 5,116,964, (*id.*, pages 16-17); and

d. the rejection of claims 15, 36, 38, 40, and 41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,408,038 in view of U.S. Patent No. 5,824,784, (*id.*, pages 18-20).

In addition, claims 9, 10, 15, 16, 36-43, and 46-49 are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. (*Id.*, page 20).

Applicants have amended claims 9, 10, 15, and 16 to replace each occurrence of the phrase "has an activity of the polypeptide as set forth in SEQ ID NO:2" with the phrase "inhibits T cell activation of monocytes." Inhibiting T cell activation of monocytes is supported by the application as filed and adds no new matter. *See, e.g.,* Specification, page 2, lines 6-7.

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Formal Matters

The Examiner advises Applicants "that should claim 9 be found allowable, claim 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof." (Final Action, page 2).

Applicants respectfully note that claims 9 and 10 are product-by-process claims and that the processes encompassed by each claim are different. For example, claim 9 recites a process comprising culturing a eukaryotic cell comprising a vector. In contrast, claim 10 recites a process comprising culturing a prokaryotic cell comprising a vector. Thus, the cells according to claim 9 are different from those according to claim 10. For at least these reasons, the two claims are not substantial duplicates.

The Claims Are Enabled

Claims 9, 10, 15-17, 36-43, and 46-49 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. (Final Action, pages 2-11). According to the Office, the specification does not enable one skilled in the art "to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No. 13."[1] (*Id.*, page 3, emphasis original).

Applicants respectfully traverse. Applicants incorporate by reference all prior comments that respond to the Examiner's prior arguments in Paper No. 13. Applicants also now respond to the Examiner's new arguments in the four paragraphs spanning pages 10 to 11 of the Final Action.

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[1] The Examiner repeats verbatim text from Paper No. 13 (i.e., the previous Office Action mailed October 22, 2002) from the last paragraph at the bottom of page 3 through the second full paragraph on page 9 of the Final Action. Applicants responded to these arguments in the Amendment filed April 16, 2003.

As Applicants stated in the Amendment filed April 16, 2003, 35 U.S.C. § 112, first paragraph, requires that a patent application adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 52 U.S.P.Q.2d 1129, 1136 (Fed. Cir. 1999). Applicants again submit that the Examiner has not met her initial burden to establish a reasonable basis to question the enablement of claims 9, 10, 15-17, 36-43, and 46-49. *See* M.P.E.P. § 2164.04 (citing *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)).

> [A] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support.

In re Marzocchi, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis in original); *see also* M.P.E.P. § 2164.04.

Here, the Examiner acknowledges that the specification enables the following aspects of the invention:

- an isolated apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment produced by a process comprising culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of a nucleotide sequence selected from the nucleotide sequences set forth in claim 9 subparts (a) through (h) and (j);
- an isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment encoded by a nucleic acid molecule consisting essentially of a

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nucleotide sequence selected from the nucleotide sequences set forth in claim 16 subparts a(2) through a(8) and b(2) through b(9); and

- an isolated apo-A-1 fragment T cell activation inhibitor-like polypeptide fragment consisting essentially of an amino acid sequence selected from: claim 15 subparts (a) through (f);

(Final Action, page 2). In addition, the Examiner acknowledges that the specification enables (1) compositions comprising these polypeptide fragments and a pharmaceutically acceptable carrier and (2) fusion polypeptides comprising these polypeptides and an IgG constant domain for inhibiting the production of IL-I and TNF alpha *in vitro* in THP- 1 cells activated by membranes of stimulated HUT-78 cells. (*Id.*)[2]

According to the Examiner, however, the specification does not enable one skilled in the art to make or use the full scope of apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragments encoded by nucleic acid molecules that hybridize to or otherwise share certain percent identity with the specific sequences in claims 9 and 16 that admittedly are enabled. (*Id.*, page 3). Similarly, the Examiner asserts that the specification does not enable one skilled in the art to make or use the full scope of apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragments that are orthologs of

[2] The Examiner does not indicate that any aspects of claim 10 or of claims 40-43 are enabled. Logically, however, the specification must enable an isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment produced by a process comprising culturing a prokaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of a nucleotide sequence selected from the nucleotide sequences set forth in claim 10 subparts (a) through (h) and (j). These subparts of claim 10 are identical to those the Examiner acknowledges to be enabled in claim 9, except that in claim 10 the nucleic acid is expressed in a prokaryotic cell rather than in a eukaryotic cell. Also, it seems that the specification must enable certain covalently

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or share a certain percent identity with the specific sequences in claim 15 that admittedly are enabled. (*Id.*)

To the extent the Examiner supports her position on enablement by repeating verbatim positions (e.g., regarding the meaning of the transitional phrase "consisting essentially of," the relevance of Attwood et al., or the selective application of some but not all of the factors enumerated in *In re Wands*) set out in the Office Action mailed October 22, 2002, , Applicants incorporate by reference their responses to those positions in the Amendment filed April 16, 2003. Applicants respectfully request that the Examiner respond to their earlier arguments, as supplemented herein, by either modifying her contentions or explaining why she believes that Applicants' positions are incorrect.

In particular, however, Applicants wish to further address the Examiner's position that, because Applicants have explicitly disclosed only human apo A-I sequences, one skilled in the art would have to engage in undue experimentation to make and use any other AFTI polypeptide fragment. (*See, e.g.* Final Action, page 10). As Applicants stated in the Amendment filed April 16, 2003, 452 apo A-I protein sequences and 1484 apo A-I nucleotide sequences from a variety of species are immediately retrievable from the GenBank online database. (Page 13). One skilled in the art of the invention, by comparing these sequences with the disclosed human AFTI sequences, could easily identify nonhuman AFTI polypeptides and nucleic acids. This type of analysis is routine in the art regardless of whether the skilled artisan is searching for (1) sequences with a

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modified polypeptides according to claims 40-43 for the same reason(s) the Examiner concludes that certain compositions and fusion proteins are enabled.

particular percent identity to the disclosed AFTI sequences (e.g., claims 9(k), 10(k),15(g), 16(a)); (2) allelic or splice variants of the disclosed AFTI sequences (e.g., claims 9(l), 10(l), 15(i) 16(b); (3) orthologs of the disclosed AFTI sequences (e.g., claim 15(f)); or (4) fragments of the disclosed AFTI sequences (e.g., claims 9(m), 9(n), 10(m), 10(n), 15(h), 16(c), 16(d)). Moreover, one skilled in the art, using the AFTI activity assay taught in the Examples, could readily confirm that the sequences identified in this manner had the claimed activity. (Applicants have amended claims 9, 10, 15, and 16 to recite, where appropriate, that the AFTI polypeptide "inhibits T cell activation of monocytes." The rejection of these claims as not being enabled because the activity was "unspecified" (*see, e.g.*, Final Action, page 10) is moot. The Examiner has provided nothing but bare assertions that this work would involve undue experimentation.

In addition, Applicants wish to address several new issues that allegedly support the rejection of claims 9, 10, 15-17, 36-43, and 46-49 as not being enabled. First, the Examiner argues that claims 9, 10, 15-17, 36-43, and 46-49 are not enabled because they recite AFTI nucleotide or peptide sequences that are at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to at least one of the disclosed human AFTI sequences. In the previous Office Action mailed October 22, 2002, the Examiner asserted that such claims were not enabled because "the specification does not disclose the specific conditions used by applicants such as salt concentration, melting and annealing temperature and the duration of hybridization for the specific polynucleotide encoding the specific polypeptide." (Page 8.) In response, Applicants directed the Examiner's attention to pages 21-23 of the specification, which provide a

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detailed description of hybridization conditions that are "highly" or "moderately" stringent. (Amendment filed April 16, 2003, page 14). Now, the Examiner contends that, to satisfy 35 U.S.C. § 112, first paragraph, the claims must actually recite specific hybridization conditions. (Final Action, page 10).

Applicants are unaware of any statute or caselaw that supports the Examiner's position. Applicants have defined the terms "highly stringent" (specification, page 21, lines 10-20) and "moderately stringent" (specification, page 22, lines 13-19). Moreover, the specification provides guidance as to what conditions are "highly stringent" (specification, page 21, lines 10-20) and "moderately stringent" (specification, page 22, lines 13-19). The law requires no more.

Second, the Examiner observes that the specification defines AFTI polypeptide variants as "AFTI polypeptides comprising amino acid sequences having one or more amino acid substitutions, deletions, additions . . . the variants have from 1 to 3[3] or more than 100 amino acid substitutions, insertions, additions and/or deletions." (Final Action, page 10, ellipses original). According to the Examiner, "there is no guidance in the specification as to which amino acids within the amino acid sequence (polypeptide) of SEQ ID NO: 2, the corresponding polynucleotide can substitute, added or deleted and whether the resulting polypeptide would retain the structure and function as SEQ ID NO: 2." (*Id.*) Applicants presume that the Examiner concludes, based on the alleged lack of guidance, that claims 9, 10, 15-17, 36-43, and 46-49 are not enabled.

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[3] The Examiner has deleted language specifying eight intervening ranges without indicating that she has done so.

Without taking a position on the Examiner's presumed conclusion, Applicants note that none of the claims under consideration recite the term "polypeptide variant." Instead, the claims encompass "allelic variants" and "splice variants" of the disclosed AFTI sequences. The specification separately defines these terms, making it clear that both refer to naturally occurring variants of the disclosed sequences. (Pages 14-15). The skilled artisan requires no guidance in order to make naturally occurring allelic and splice variants of AFTI sequences, which, because they are naturally occurring, are extremely likely, if not certain, to retain the required activity.

Finally, the Examiner asserts that "[g]iven the indefinite number of undisclosed 'heterologous amino sequence [sic]', it is unpredictable which fusion protein comprising any undisclosed 'heterologous amino acid sequence' and polypeptide such as the ones recited in claim 15 would have the same function as SEQ ID NO: 2 [sic, and], in turn, would be useful for any purpose." (Final Action, page 11).

Applicants' undersigned representative performed a search of the U.S. Patent and Trademark Office database on September 30, 2003, for issued patents presenting claims that contain the phrase "fusion protein." The search identified 1541 patents with this term in the claims. A copy of the first page of the search results is enclosed as an attachment to this Amendment. A review of the first ten patents on the list showed that eight of them claimed "fusion proteins" with no limitation whatsoever on the identity of the "heterologous amino acid sequence." The Examiner has provided no basis for concluding that the properties of AFTI fusion proteins are more unpredictable than those of the multitude of patented fusion proteins, and cannot credibly reject the instant claims on this basis.

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Based on the above, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled.

The Claims Are Supported by the Specification

Claims 9, 10, 15-17, 36-43, and 46-49 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Final Action, page 11.). According to the Examiner, the specification does not provide written description support for the same claim limitations that it allegedly does not enable. (*Id.*, pages 11-12).

Applicants respectfully traverse. As Applicants noted in the Amendment filed April 16, 2003, the Examiner bears the burden of "presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims." M.P.E.P. § 2163(II)(A). Where the claims in question are the original claims, "there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." *Id.* (citing *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)).

Also as noted in the Amendment filed April 16, 2003, Applicants have explicitly described three nucleic acid sequences (nucleotides 73 to 601, 73 to 451, and 485 to 820 in SEQ ID NO:1) that encode AFTI polypeptide fragments according to the invention. (Page 20). Applicants also have explicitly described five amino acid sequences (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113, and 156 to 267 in SEQ

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ID NO:2) that are AFTI polypeptide fragments according to the invention. (*Id.*) According to the Examiner, these eight embodiments of the invention are a single "species" because they are all derived from human apo A-I. (Final Action, page 13). The Examiner relies on *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), for the proposition that "[g]iven the lack of additional fragment[s] from other species, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus." (*Id.*, page 14).

Here, Applicants, have disclosed eight species within the claims. That all eight species are derived from a single organism is irrelevant. Moreover, the specification unambiguously teaches that the invention encompasses AFTI polypeptides derived from nonhuman sources. For example, the specification states:

> The term "AFTI polypeptide ortholog" refers to a polypeptide from another species that corresponds to an AFTI polypeptide amino acid sequence specifically described herein. For example, mouse and human AFTI polypeptides are considered orthologs of each other.

(Page 15, lines 24-27). Also, these nonhuman AFTI polypeptides were specifically claimed in the original claims, *see, e.g.*, claim 15, and are entitled to a strong presumption that they are supported by the as-filed application.

The situation in *Lilly* was different. There, the application disclosed the sequence of a cDNA encoding rat insulin. *See Eli Lilly*, 119 F.3d at 1562. Based on the disclosure of the rat sequence, the applicants claimed human, mammalian, and vertebrate insulin cDNAs, which had not yet been isolated. *See id.* Because the application provided no information concerning the chemical structure of human,

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mammalian, and vertebrate insulin cDNAs and because one skilled in the art could not envision that structure from the name cDNA, the court found the claims invalid for lack of written description support. *See id.* at 1567-68.

Here, in contrast to *Lilly*, hundreds, if not thousands, of sequences from which AFTI polypeptides may be prepared are known to the art. Applicants are not claiming, as was the case in *Lilly*, structurally uncharacterized cDNAs encoding apo A-I proteins from different species. Instead, Applicants, are claiming polypeptide fragments of previously unknown activity that can be prepared from any of the multitude of apo A-I species known to those skilled in the art. Applicants description of eight embodiments of the invention satisfies the requirement that one skilled in the art would recognize that the inventors had possession of the claimed invention. Moreover, one skilled in the art could readily envision the chemical structure of AFTI polypeptides derived from nonhuman sources based on Applicants' disclosure of the human AFTI species. The Examiner has introduced no evidence to the contrary.

The Examiner advances several other positions to try to support her rejection of claims 9, 10, 15-17, 36-43, and 46-49 as allegedly not adequately supported by the application as-filed. First, the Examiner notes that "[w]ith regard to hybridization, the specific moderately or the specific highly stringent conditions used by Applicants such as the ones disclose[d] on page[s] 21-23 are not recite[d] in the claims." (Final Action, page 13). Applicants do not believe that the Examiner can appropriately reject a claim for lack of written description based on what that claim does not recite. Here, the terms "moderately stringent" and "highly stringent," which are used in the claims, are

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thoroughly defined (see above) in the specification. No more is needed to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Second, the Examiner asserts that there is insufficient written description of which "amino acids within the amino acid sequence (polypeptide) of SEQ ID NO: 2, and the corresponding polynucleotide can substitute, added or deleted and whether the resulting polypeptide would retain the structure and function as SEQ ID NO: 2." (Final Action, page 14). Although Applicants disagree with the Examiner's conclusion that there is insufficient written description of amino acid substitutions, additions, and deletions, they again assert that the claims do not require written description of this subject matter with respect to the claim recitations of AFTI splice and allelic variants that do not require any such modifications.

Next, the Examiner improperly states that the application as-filed does not adequately describe sequences with various percent identities to AFTI polypeptides derived from human apo A-I (i.e., SEQ ID NO: 2). (Final Action, page 14). Again, however, hundreds of protein sequences and thousands of nucleotide sequences with various percent identities to human apo A-I are known in the art (see above). No more is needed to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 9, 10, 15-17, 36-43, and 46-49 under 35 U.S.C. § 112, first paragraph, as allegedly not meeting the written description requirement.

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The Claims Are Not Anticipated

Claims 15 and 46 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,408,038 ("the '038 patent). (Final Action, page 14). According to the Examiner, the '038 patent "teaches a fusion polypeptide such as A-I/B-100 comprising the polypeptide fragment consisting of amino acid sequence from about residue 19 to 240 of SEQ ID NO: 3 fused to a heterologous sequence such as the reference SEQ ID NO: 1 (Apo B-100)." (*Id.*) The Examiner further contends that the term "consisting essentially of" expands the instantly claimed amino acid sequence residues 25 to 194 of SEQ ID NO: 2 to read on the residues 19 to 240 of SEQ ID NO: 3 in the '038 patent. (*Id.*) The Examiner also asserts that "[t]he reference polypeptide fragment comprises at least 25 amino acid residues of the claimed residue 25 to 194 of the claimed SEQ ID NO: 2 since 240 minus 19 is 221 amino acids, which is at least 25 amino acids. (*Id.*, pages 14-15).

Applicants respectfully traverse. In order to anticipate a claim, a prior art reference must teach every limitation of the claim. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986) ("It is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention, and that such a determination is one of fact."). According to the Examiner, the '038 patent discloses fusion proteins. (Final Action, page 14). Also according to the Examiner, the '038 patent discloses the sequence of human apo A-I. (*Id.*) Because claim 15 does not claim fusion proteins and does not claim full-length human apo A-I, the '038 patent cannot anticipate claim 15.

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Although the Examiner continues to insist that claims reciting "consisting essentially of" are open-ended, this is simply not the law. The phrase "'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." M.P.E.P. § 2111.03 (citing *In re Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976)) (emphasis in original). The Examiner's assertion that the phrase "consisting essentially of" somehow expands claim 15 to encompass fusion proteins simply is not credible. *See Eli Lilly*, 119 F.3d at 1573 (noting that the Examiner was correct in interpreting a claim reciting "human [proinsulin] ***consisting essentially of*** a plus strand having the sequence [nucleotides that encode human proinsulin]" to exclude fusion proteins) (emphasis in original).

Claim 46 recites "[a] fusion polypeptide comprising the polypeptide according to claim 15 and a heterologous amino acid sequence." A review of the '038 patent identifies two fusion proteins containing human apo A-I sequences. One of these contains (henceforth "fusion protein 1") "from about [amino acid] residue 120 through about residue 135 operatively linked" to a second amino acid sequence derived from apo B-100. Col. 6, lines 61-66. This fusion protein contains about 15 amino acids derived from human apo A-I. The second fusion protein (henceforth "fusion protein 2") contains amino acid sequence derived from apo B-100 "operatively linked to the amino acid residue sequence of apo A-I from about residue 19 through about residue 250 of" human apo A-I. Col. 7, lines 6-11. This fusion protein contains about 232 amino acids derived from human apo A-I.

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The smallest AFTI polypeptide of the fusion protein literally encompassed by claim 46 is "about 25 amino acid residues." *See* claim 46 and the claim from which it depends, claim 15(h). Although that polypeptide may include residues 120-135 of the '038 patent, it is 67% larger than the apo A-I portion of fusion protein 1 of the '038 patent. The largest AFTI polypeptide literally encompassed by claim 46 is about 170 amino acid residues. *See* claim 46 and the claim from which it depends, claim 15(a). Although these residues are present in fusion protein 2 of the '038 patent, the apo A-I portion of fusion protein 2 is 36% larger than the largest AFTI polypeptide recited in claim 46.

Without evidence, the Examiner simply concludes that those large differences in size do not materially effect the basic and novel characteristics of the AFTI polypeptide fusion proteins of instant claim 46 and, therefore, are permitted by the phrase "consisting essentially of." The Examiner appears to reach this result because "[t]he reference polypeptide of SEQ ID NO: 3 [in the '038 patent] inherently has the same activity as the claimed SEQ ID NO: 2 since it is identical to the claimed SEQ ID NO: 2 and the specific activity is not recited in the claim." (Final Action, page 15).

The question, however, is not whether it is reasonable to conclude that the proteins of SEQ ID NO: 3 in the '038 patent and SEQ ID NO:2 in the instant application have the same activity. Instead, the question is whether the '038 patent teaches the recited activity of the polypeptide fragments of claim 46. Applicants assert that, at least because of (1) the differences in the sizes of the apo A-I sequences taught by the '038 patent and the instant specification and (2) the '038 patent's failure to teach the recited activity, the answer is "no.".

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Applicants respectfully request reconsideration and withdrawal of the rejection of claims 15 and 46 under § 102(b) in view of the '038 patent.

The Claims Are Not Obvious

The Examiner rejects claims 15, 46, and 47 under 35 U.S.C. § 103(a) as allegedly being obvious over the '038 patent in view of U.S. Patent No. 5,116,964 ("the '964 patent"). (Final Action, page 16). According to the Examiner, the '038 patent teaches that apo A-I is unstable. (*Id.*) Also according to the Examiner, the '964 patent teaches fusion proteins comprising the CH2 and CH3 constant domains of immunoglobulins to extend the half life of a fusion protein and, therefore, supplies the missing element. (*Id.*) The Examiner states "it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the LHR of the immunoglobulin fusion polypeptide as taught by the '964 patent or the B-100 polypeptide in the A-I/B-I00 fusion protein as taught by the '038 patent for a fusion protein comprising apo A-I fused to IgG constant or fragment thereof as taught by the '038 patent and the '964 patent." (*Id.*)

Applicants respectfully traverse. As an initial matter, claim 15 does not claim fusion proteins and does not claim human apo A-I. For the same reason that the '038 patent cannot anticipate claim 15 (see above), the combination of the '038 patent with the '964 patent cannot render claim 15 obvious.

Moreover, the Examiner has failed to establish a *prima facie* case of obviousnessness with respect to claims 46 and 47. To establish a *prima facie* case of obviousness, the Examiner must identify some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

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the art, to combine the references as proposed. *See* M.P.E.P. § 2142. Moreover, there must be a reasonable expectation of success. *See id.* Finally, the references must teach or suggest all of the claim limitations. *See id.* However, if the proposed combination of references would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *See* M.P.E.P. § 2143.01.

Here, the Examiner has failed to identify the required motivation to combine the '038 and '964 patents to make the invention claimed in claims 46 and 47 (and 15). The Examiner asserts that one of ordinary skill in the art would have been motivated to make fusion proteins comprising an AFTI polypeptide according to claim 15 and immunoglobulin constant domains because the '038 patent teaches that apo A-I is unstable. (Final Action, page 16). In fact, the '038 patent states only that the "immunochemical characterization of native apo A-I, i.e., apo A-I as it is found on HDL particles, has been problematic because of its antigenic heterogeneity and instability. Col. 2, lines 5-8. In other words, the '038 patent indicates that complexes of apo A-I and HDL are unstable, not that apo A-I itself is unstable. Even assuming that the '038 patent did disclose that apo A-I itself was unstable, the Examiner has provided no basis for concluding that this has any relevance to the stability of AFTI polypeptides. Applicants identified the activity of these polypeptides in human serum indicating that the polypeptides are stable. *See* Specification, page 96.

Additionally, replacing the apo B-100 portion of the fusion proteins disclosed by the '038 patent with the immunoglobulin constant regions of the '964 patent would

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impermissibly change the principle of operation of the '038 patent's invention. According to the '038 patent:

> The present invention relates to assays of lipoprotein markers for abnormal lipid metabolism. The invention particularly relates to assays of human plasma for lipoproteins containing apoproteins B-100 and A-I, and the use of a polypeptide that contains a pan epitope of at least the apo B-100 protein along with antibodies that immunoreact with at least that epitope.

Col. 1, lines 19-25. To achieve this end, the '038 patent provides fusion proteins that react with both antibodies directed against apo A-I and antibodies directed against apo B-100. By replacing the apo B-100 portions of the fusion proteins with immunoglobulin constant regions (or anything else), one would render the fusion proteins of the '038 patent inoperative for their intended use in immunoassays.

The Examiner has failed to establish a *prima facia* obviousness case. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 15, 46, and 47 under 35 U.S.C. § 103(a) as allegedly unpatentable over the '038 patent in view of the '964 patent.

The Examiner also rejects claims 15, 36, 38, 40, and 41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '038 patent in view of U.S. Patent No. 5,824,784 ("the '784 patent"). (Final Action, page 18). According to the Examiner, "[t]he '784 patent teaches method and composition for covalently modified [sic] any polypeptide of interest such as G-CSF or INF with a water-soluble polymer," including those recited in the rejected claims. (*Id.*) The Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified [sic] the A-I/B-100 fusion protein as taught by the '038 patent using

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[a] water soluble polymer as taught by the '784 patent for a water-soluble polymer modified A-I/B-100 as taught by the '038 patent and the '784 patent. (*Id.*)

Applicants respectfully traverse. Applicants again note that claim 15 does not claim fusion proteins and does not claim full-length human apo A-I. For the same reason that the '038 patent cannot anticipate claim 15 (see above), the combination of the '038 patent with the '784 patent cannot render claim 15 obvious. Specifically, regardless of any alleged teachings of the '784 patent concerning polymers, the Examiner has not established that the '038 patent would have suggested the AFTI polypeptides claimed in claim 15. This is also true of claims 36, 38, 40, and 41, which, like claim 15, do not claim fusion proteins or full-length apo A-I. For these reasons, Applicants need not address the Examiner's allegations about the '784 patent and do not acquiesce to those allegations.

Moreover, even if the rejected claims were directed to fusion proteins, the Examiner has pointed to nothing that would motivate one of ordinary skill in the art to modify the apo A-I/apo B-100 fusion proteins of the '038 patent with water-soluble polymers. The '038 patent discusses, *inter alia*, fusion proteins for use in immunoassays. (See above). Neither the '038 patent nor the '784 patent suggests a need to increase the stability of the fusion proteins used in immunoassays. Nor has the Examiner pointed to any general knowledge that would motivate one of ordinary skill in the art to modify the stability of such fusion proteins. In fact, by modifying the fusion proteins disclosed in the '038 patent using the methods of the '784 patent, one of ordinary skill in the art would expect to decrease their immunogenicity (*see* '784 patent, col. 1, lines 19-33) and, therefore, their usefulness for their intended purpose.

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For these reasons, the Examiner has failed to establish a *prima facia* obviousness case. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 15, 36, 38, 40, and 41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '038 patent in view of the '784 patent.

The Claims Are Definite

Finally, the Examiner newly rejects claims 9, 10, 15, 16, 36-43, and 46-49 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for their recitation of a broad limitation (i.e., "comprising") together with a narrow limitation (i.e., "consisting essentially of"). (Final Action., page 20). The Examiner asserts that "Applicant's amendment necessitated the new ground(s) of rejection." (*Id.*) According to the Examiner, claims 9, 10, 15, and 16 recite the broad element "nucleotide sequence selected from at least comprising [sic] one of (k), (l), and (m) comprising a fragment of at least about 16 nucleotides." (*Id.*) The Examiner contends that the same claims also recite the allegedly narrower element "nucleotide sequence consisting essentially of a nucleotide sequence selected from the nucleotide sequence (k), (l), and (m)." (*Id.*)

Applicants respectfully traverse. As an initial matter, Applicants note that the Amendment filed April 16, 2003, did not add the language the Examiner now asserts to be indefinite. That language was present in the rejected claims before they were amended by virtue of their dependence from other claims. (*See* Amendment filed April 16, 2003, page 10, "Applicants have amended claims 9, 10, and 16 to incorporate the limitations of the nonelected claims from which they originally depended."). Claim 15 was amended only in the preamble and to correct an error identified by the Examiner. The remaining newly rejected claims (i.e., claims 36-43 and 46-49) depend from either

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claim 15 or 16 and have not been amended. The Examiner's assertion that Applicant's amendment necessitated this new ground of rejection is incorrect. The new rejection is improper in a final Office Action and either the rejection or the finality of the Office Action should be withdrawn. *See* M.P.E.P. § 706.07(a).

Moreover, the claims actually recite "a nucleotide sequence consisting essentially of . . . (n) a nucleotide sequence selected from at least one of (k), (l), and (m) comprising a fragment of at least about 16 nucleotides." *See, e.g.*, claim 9. The language allegedly quoted by the Examiner is not present in claims 9, 10, 15, or 16. (In fact, claim 15, which recites amino acid sequences, does not use the word "nucleotide" at all.) Element (n) in claim 9 (and similar elements in claims 10, 15, and 16) is not indefinite in simply specifying that the nucleotide sequences of (k), (l), and (m) must be at least 16 nucleotides long. This is entirely different from the cases relied on by the Examiner, which address the treatment under 35 U.S.C. § 112, second paragraph of claims that recite closed transitional phrases with phrases like "such as," which offer only suggestions for those elements within the claim.[4]

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 9, 10, 15, 16, 36-43, and 46-49 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

SUMMARY

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[4] Applicants note that the Examiner appears to have misunderstood *Ex parte Wu*, 10 U.S.P.Q.2d 2031 (Bd. Pat. App. & Inter. 1989). In *Wu*, the Board refused to find a claim indefinite for reciting the closed transitional phrase "consisting of" with the phrase "optionally." *See id.* at 2033-34. According to the Board, the claim was not indefinite because the "optional" element was explicitly set forth as within the invention. *See id.*

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 9, 10, 15-17, 36-43, and 46-49 in condition for allowance. Applicants submit that the proposed amendments of claims 9, 10, 15, and 16 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Moreover, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Applicants request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: October 2, 2003

By: _____
William L. Strauss
Reg. No. 47,114

Attachments: **Patent Database Search Results (3 pages)**

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Searching 1976 to present...

Results of Search in 1976 to present db for:
ACLM/"fusion protein": 1541 patents.
*Hits 1 through **50** out of **1541***

Next 50 Hits

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Refine Search ACLM/"fusion protein"

	PAT. NO.	Title
1	6,627,728	Compounds from moraxella catarrhalis
2	6,627,204	Polynucleotides and polypeptides BASB033 from neisseria meningitidis and their uses
3	6,627,202	HBV core antigen particles with multiple immunogenic components attached via peptide ligands
4	6,624,184	Amide and diamide inhibitors of IMPDH enzyme for use in treating IMPDH-associated disorders
5	6,623,940	Expression vectors encoding bispecific fusion proteins and methods of producing biologically active bispecific fusion proteins in a mammalian cell
6	6,620,909	Adipocyte complement related protein homolog zacrp2
7	6,617,135	Multiple cytokine protein complexes
8	6,617,134	Dimer of molecular variant of apolipoprotein and processes for the production thereof
9	6,613,746	AGP-antibody fusion proteins and related molecules and methods

10 6,613,337 Leishmania antigens for use in the therapy and diagnosis of leishmaniasis
11 6,613,335 Polypeptides from moraxella (branhamella) catarrhalis
12 6,613,331 Vaccine against Lyme disease
13 6,613,327 Methods of preventing immune-mediated abortion by inhibiting a CD28-mediated costimulatory signal
14 6,610,508 Translation driver system and methods for use thereof
15 6,610,495 Method for detecting proteinaceous inhibitors of protein-protein or DNA-protein interactions
16 6,610,485 Methods for isolating a cDNA encoding a membrane-bound protein
17 6,610,479 Activating a reversibly inactivated immobilized enzyme by release from an immobilizing moiety
18 6,608,182 Human vascular endothelial growth factor 2
19 6,607,881 Combined ligand and receptor display
20 6,607,880 Methods and reagents for modulating apoptosis
21 6,607,731 Leishmania antigens for use in the therapy and diagnosis of leishmaniasis
22 6,607,728 Compounds and methods for the diagnosis and treatment of ehrlichia infection
23 6,607,724 Compositions and methods for inhibiting angiogenesis
24 6,605,706 Method for producing a correctly folded, biological active recombinant protein
25 6,605,699 Galectin-11 polypeptides
26 6,605,467 Fusion protein comprising the whole or part of the PP65 protein of human CMV, useable in particular for preparing a vaccine
27 6,602,684 Glycosylation engineering of antibodies for improving antibody-dependent cellular cytotoxicity
28 6,602,677 Thermostable luciferases and methods of production
29 6,600,029 Metabolic engineering of polyhydroxyalkanoate monomer synthases
30 6,600,018 Secreted frizzled related protein, sFRP, fragments and methods of use thereof
31 6,600,013 Moraxella catarrhalis BASB034 polypeptides and uses thereof
32 6,596,522 Detection of transmembrane potentials by optical methods
33 6,596,509 Recombinant constructs and systems for secretion of proteins via type III secretion systems
34 6,596,485 Green fluorescent protein fusions with random peptides
35 6,596,475 Protein conjugates containing multimers of green fluorescent protein
36 6,596,281 Mycobacterium tuberculosis specific proteins and genes, mixtures of antigens and uses thereof
37 6,596,269 Methods of treating chronic pain
38 6,593,456 Tumor necrosis factor receptor releasing enzyme
39 6,593,299 Compositions and methods for controlling pests

40 6,593,083 T Hepatitis C assay utilizing recombinant antigens
41 6,592,877 T Compounds and methods for immunotherapy and diagnosis of tuberculosis
42 6,590,076 T Compositions for the treatment and diagnosis of breast cancer and methods for their use
43 6,589,730 T Methods for identifying protein-protein interactions by selective transduction
44 6,586,572 T Compositions and methods for the therapy and diagnosis of breast cancer
45 6,586,411 T System for monitoring the location of transgenes
46 6,586,384 T Method of treating fabrics and apparatus used therein
47 6,586,240 T Visualization of RNA in living cells
48 6,582,934 T Recombinant DNA encoding an epidermal growth factor receptor related protein
49 6,582,927 T Method for detecting protein-protein interactions and a kit therefor
50 6,579,973 T Compositions for the treatment and diagnosis of breast cancer and methods for their use

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